Report of Eight Recent Cases of Locally Advanced Primary Pulmonary Artery Sarcomas: Failure of Doxorubicin-Based Chemotherapy

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Background: Case reports of primary pulmonary artery sarcomas are very rare.

Methods: We described herein eight new cases diagnosed between December 2000 and December 2004.

Results: There were four men and four women, with median age of 52 years. Presenting symptoms mimicked pulmonary emboli in all cases. There were six "intimal sarcomas" and two leiomyosarcomas. In six cases, we observed initial metastasis in lung (six cases), in bone (two cases), and in brain (two cases), and adrenal gland (one case). The palliative treatments included surgical desobstruction (six cases), conformational radiotherapy (four cases), and chemotherapy (seven cases). Doxorubicin-based regimen failed in seven cases. All patients died (median survival: 8 months, extremes 5–20 months).

Conclusion: Those eight cases illustrate the high incidence of initial metastasis and the very poor outcome of primary pulmonary artery sarcomas despite classic doxorubicin-based chemotherapy.

Key Words: Sarcoma, Soft tissue sarcoma, Metastases, Pulmonary artery, Outcome, Doxorubicin.

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Primary pulmonary artery sarcoma (PPAS) is an exceptional cancer. Its estimated incidence is about 0.001 to 0.003%.[1–3] Data about its clinical outcome are very spare. Since its first description in 1923, literature data consists in about 150 cases.[1–4] Few years ago, because of the rarity of this tumor and its nonspecific presenting symptoms, this diagnosis was usually postmortem. New imaging techniques (such as transesophageal echocardiography, helicoidal computed tomography [CT], and magnetic resonance imaging [MRI]) play a key role in diagnosis and preoperative assessment of PPAS. Well-planned large en bloc resection of tumor is the treatment of choice. Nevertheless, despite surgery, the prognosis of PPAS is poor, because most of those tumors develop metastasis. We describe herein the outcome of eight consecutive locally advanced PPAS.

PATIENTS AND METHODS

The Oscar Lambret Cancer Centre is the comprehensive Cancer Centre of northern France. About 950 adult patients with soft tissue or visceral sarcoma were treated from December 2000 to December 2007. Among those 950 patients, eight presented a case of biopsy-proven PPAS. The records of those patients were available for review and were retrospectively analyzed.

RESULTS

There were four men and four women. The median age at the time of diagnosis was 52 years (range, 47–59). Two patients had tobacco consumption history. In all cases, presenting symptom mimicked a "pulmonary embolism." Two of them experienced paraneoplastic fever (Table 1). In three cases, MRI suggested diagnosis of PPAS before surgical exploration. In seven cases, histologic diagnosis was established by analysis of specimen obtained by emergency surgical exploration. In one case, diagnosis was obtained by biopsy of lung metastasis. In six cases, the histologic subtype was "spindle-cells sarcoma without differentiation" ("intimal sarcoma"). The two others PPAS were classified as differentiated leiomyosarcoma.

Only one patient (case 1) was free of metastasis at initial diagnosis.

In six cases, PPAS were associated with concomitant metastasis: lung metastasis (seven patients), mediastinal lymph node metastasis (two patients), bone metastasis (two patients), cerebral metastasis (two patients), and adrenal metastasis (two patients).

Only one patient (case 1) underwent initial complete resection (resection of trunk of artery pulmonary associated with total pneumonectomy). Six patients received palliative surgical desobstruction, followed by radiotherapy (50–54 Grays) in four cases.

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TABLE 1. Outcome of Eight Recent Primary Pulmonary Artery Sarcoma

Case	Sex	Age	Presenting Symptoms	Initial Metastasis	Initial Treatment	Metachronous Metastasis	Outcome
1 (August 2003)	M	48	PH	Absent	Large resection	Lung (4 mo) Skin and liver (5 mo)	Died at 6 Mo
2 (July 2003)	F	53	PH and fever	Mediastinal lymph nodes Lung	Palliative desobstruction and radiotherapy	Cerebral (6 mo) Bone (6 mo)	Died at 8 mo
3 (September 2003)	F	47	PH	Lung (one solitary)	Palliative desobstruction	Skin and liver (8 mo)	Died at 8 mo
4 (October 2002)	F	57	PH and bone pain	Bone (spine) Cerebral	Palliative desobstruction		Died at 5 mo
5 (March 2001)	F	52	PH	Mediastinal lymph nodes Lung and pleura	Palliative desobstruction and radiotherapy	Cerebral (19 mo)	Died at 20 mo
6 (September 2001)	M	59	PH, fever, and bone pain	Bone Adrenal Cerebral Lung	Palliative desobstruction and radiotherapy	Spleen (4 mo) Liver (4 mo)	Died at 5 mo
7 (December 2004)	M	52	PH	Lung	Palliative chemotherapy	Adrenal (4 mo) Liver (4 mo)	Died at 8 mo
8 (March 2007)	M	52	PH	Lung	Palliative desobstruction, radiotherapy, and chemotherapy	Brain (8 mo) Diaphragm (8 mo) Bone (8 mo)	Died at 13 mo

PH, pulmonary hypertension.

TABLE 2. Chemotherapy Result

Case	Sex	Age	Histological Diagnosis	First-line Chemotherapy	Number of Cycles	Results	Following Treatment
2 (July 2003)	F	53	Intimal sarcoma	MAID regimen (1)	6	Apparition of cerebral and bone metastasis Stabilization of lung metastasis (2)	Second-line chemotherapy (Ifosfamide 9 g/m^2;) with progressive disease
3 (September 2003)	F	47	Intimal sarcoma	MAID regimen (1)	6	Stabilization of lung metastasis and regression of primitive tumor Apparition of skin and liver metastasis	Best supportive care
4 (October 2002)	F	57	Differentiated leiomyosarcoma	Doxorubicin alone: 75 mg/m^2;/3 wk	3	Progression of lung metastasis and primitive tumor	Best supportive care
5 (March 2001)	F	52	Differentiated leiomyosarcoma	Doxorubicin alone: 75 mg/m^2;/3 wk	3	Progression of lung metastasis (2)	Second-line chemotherapy (Ifosfamide 3 g/m^2;) with a long stabilization (10 mo)
6 (September 2001)	M	59	Intimal sarcoma	MAID regimen (1)	4	Apparition of spleen and liver metastasis Stabilization of cerebral, lung and adrenal metastasis (2)	Best supportive care
7 (December 2004)	M	52	Intimal sarcoma	MAID regimen (1)	4	Apparition of liver and adrenal metastasis Stabilization of lung metastases and primary tumor	Best supportive care
8 (March 2007)	M	52	Intimal sarcoma	Doxorubicin alone: 75 mg/m^2;/3 wk	4	Apparition of brain and diaphragmatic metastases (2)	Best supportive care

(1) MAID, doxorubicin 20 mg/m^2; (J1–J3); ifosfamide 2 g/m^2; (J1–J3); dacarbazine 300 mg/m^2; (J1–J3); and granulocyte growth factor, day 1 = day 21.
(2) Primary tumor response is not assessable because of previous radiotherapy.

Seven patients received doxorubicin-based chemotherapy regimen: doxorubicin as single agent in three cases and an association (doxorubicin-ifosfamid-dacarbazine) in the four other cases. There were no objective response and no long-lasting stabilization. The median number of front-line chemotherapy was four. During the course of the disease, we had diagnosed brain metastasis in four cases. There was no major toxicity of chemotherapy (no cardiac failure related to doxorubicin). All patients died with progressive disease. The median survival was 8 months (range, 5–20).

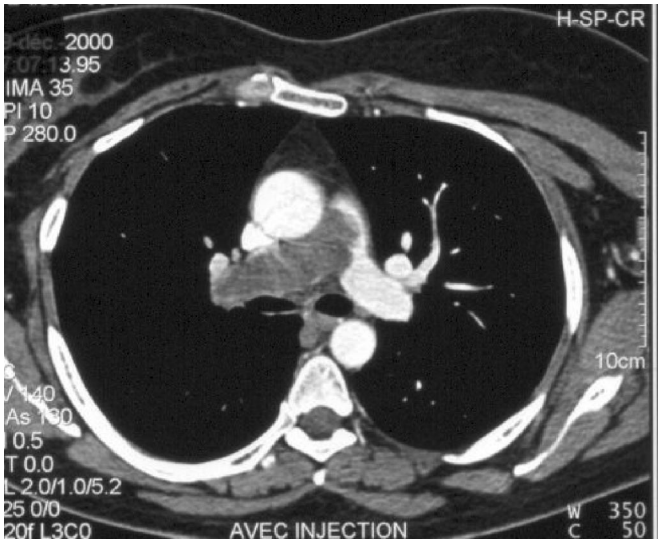

FIGURE 1. Woman, 52-year old (case 5). Helical CT with contrast: unilateral of massive perfusion defect in right pulmonary artery seems pulmonary embolism.

DISCUSSION

Presenting Signs

PPAS is an extremely rare cancer. Most of patients present between the age of 45 and 55 years, with women outnumbering men by a ratio of 2:1.[5] Few years ago, the diagnosis of PPAS was rarely established because the symptoms were insidious and nonspecific. Indeed, pulmonary embolism is the most common initial clinical diagnosis in a large series. Nevertheless, atypical features are present, such lack of predisposing factors for thromboembolism, persistence, and recurrence of symptoms despite adequate anticoagulation, and unilateral of massive perfusion defect.[6–8] Consequently, many patients were treated for weeks or months with anticoagulation before a tissue diagnosis was rendered (Figures 1, 2). The failure of anticoagulation precipitates modern imaging exploration and most of definitive diagnosis comes after surgical exploration for presumed thromboembolic disease with pathologic examination of the resected specimen. This incorrect diagnosis can delay proper therapy.

New noninvasive techniques such as transesophageal echocardiography, helicoidal CT, and MRI are more sensitive for the detection of cardiac tumors. MRI easily demonstrates the intravascular mass of PPAS and delineates intraluminal

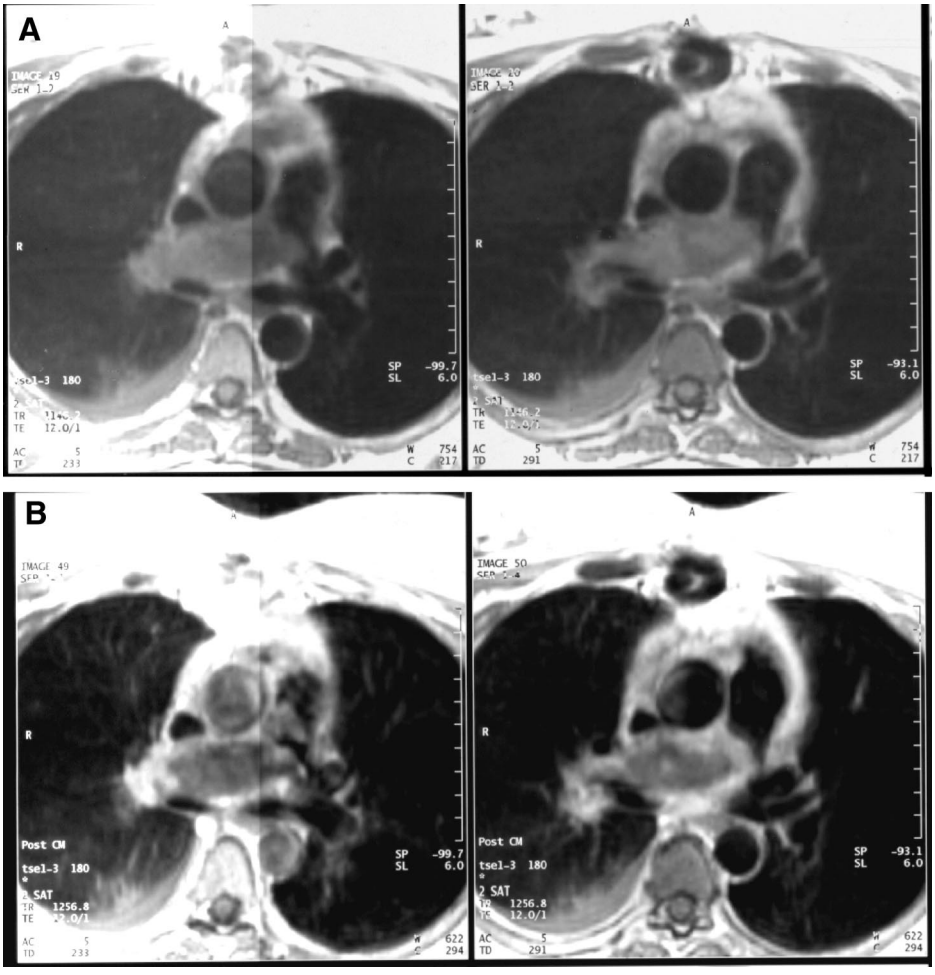

FIGURE 2. *A,* MRI performed 4 weeks later because of failure of anticoagulation. T1-weighted images show intermediate heterogeneous signal intensity in right pulmonary artery with irregular margins and superior vena cava infiltration (arrow). Right pleural effusion appears (arrow head). *B,* After contrast administration: the lesion seems heterogeneous with large central necrosis. Signal of peripheral zone is enhanced by contrast.

spread in the pulmonary arteries. In addition, MRI is well suited for the anatomic or functional demonstration of tumor extension to the pulmonary valve and involvement to the pericardium.[9] Although distinguishing an intraluminal-filling defect caused by thrombus from one caused by PPAS could be very difficult, contrast enhancements in an intraluminal mass on MRI suggest PPAS.[9,10] Extension of the tumor beyond the vessel margins clearly confirms a neoplastic etiology.[11] In a literature review in 1990, Kruger et al. found 93 cases of PPAS, with 60% diagnosed postmortem.[12] Cox et al., in 1997 found 42 additional cases with 90% diagnosed antemortem.[4] The major factor in improved diagnosis seems to be use of MRI, where enhancement of with gadolinium helps differentiate tumor from thrombus. Those techniques aid preoperative assessment. Despite these favorable imaging characteristics, distinction of PPAS from embolism has remained difficult, necessitating cytologic or histologic analysis. Nowadays, diagnosis of PPAS is made preoperatively in about 50% of cases.[11]

Histologic Diagnosis

Transbronchial lung biopsy can be helpful, but it carries the risk of bleeding in patients with pulmonary hypertension. Another technique of diagnosis is pulmonary catheter sampling; however, this technique has some technical difficulties and requires an experimented pathologist.[13] In most cases, diagnosis is obtained by analysis of resected sampling. Most of these tumors arise from primitive intimal cells. They are most conveniently grouped as "intimal sarcomas," because they show no discernible differentiation, or minimal fibroblastic, or smooth muscle differentiation. Differentiated soft tissue sarcomas are observed, such as osteosarcoma, leiomyosarcoma, angiosarcoma, or myxoid liposarcoma.[14] Main differential diagnoses are Takayashu arteritis, giant cell arteritis, fibrosing mediastinis, and extension of lung cancers or mediastinal tumors.[14]

Initial Extension

PPAS most often arise in the pulmonary trunk and may form a nodular intraluminal mass, or they may spread along the intimal surface. Retrograde spread can involve the pulmonary valve and right ventricle, whereas anterograde spread is along the pulmonary artery branches into the lung. Direct transmural spread of tumor occurs in approximately 50% of cases. Invasion of structures adjacent to the heart by tumor can causes hemoptysis or dysphonia. Initial pulmonary are present in 40% of the patients. But, emboli from these tumors to the lungs or peripheral arteries may mimics embolic disease. In our experience, seven tumors arise from pulmonary trunk and one from left pulmonary artery (case 1). In four cases, we observed large transmural extension associated with hemoptysis. Only one patient was free of metastasis at diagnosis. Seven patients had lung metastases (one solitary metastasis in only one case), and four patients had extrathoracic metastases. Excluding bone metastases, those extrathoracic metastases were asymptomatic and were discovered during systematic assessment.

Treatment

Initial complete resection is often impossible. Complete resection using resection with graft and pneumonectomy has been reported in few cases, with long remission. Nevertheless, resection is often incomplete because the advancement of the tumors. In most cases, the aim of the surgical procedure is to relieve the symptoms of cardiac chamber, valve, or major blood vessel obstruction. There is no evidence for adjuvant radiotherapy or chemotherapy, but patients with long survival had multimodal approach.[15,16] In our experience, only one patient had complete resection without adjuvant treatment. In that case, metachronous metastases were observed at 4 months. In six cases, the surgical procedure was palliative with desobstruction. In four cases, conformational radiotherapy had very good palliation on pulmonary hypertension and hemoptysis related to bronchus involvement. Seven patients received chemotherapy with doxorubicin, without efficacy. We had observed long-lasting stabilization with ifosfamide (case 5). Further chemotherapy combination should be evaluated in this indication.

Outcome and Survival

In our experience, all patients had developed metastases. All patients presented lung metastases. The occurrence of brain metastases is high in comparison with other location of soft tissue sarcoma. Sarcomas of all types accounted for less than 3% of brain metastases in an autopsy series reported in 1964.[17] The median survival of PPAS is classically 8 months. The mean survival after diagnosis without treatment is short with only 1.5 months, but can be considerably extended by total excision of the tumor. Moffat et al. reported on survival rates ranging from a few weeks up to 3.5 years.[18,19] Recent data indicate a survival of even 10 years or more after complete surgical resection, so that, the operative procedure should be favored whenever possible.[20,21]

CONCLUSION

PPAS is rare. Presenting symptoms are nonspecific. MRI allows obtaining precocious diagnosis.[4] We observe that initial systemic extension is very frequent. Recent data indicate that long survival is obtained by large complete resection in a multimodal approach. Nevertheless, we observed that initial or rapid metachronous metastasis is frequent, particularly in brain. In those cases, classic doxorubicin-based regimen seems ineffective.

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